



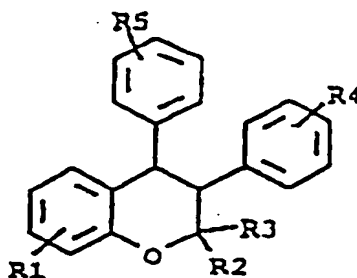
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(54) Title: USE OF 3,4-DIPHENYL CHROMANS FOR THE MANUFACTURE OF A PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OR PROPHYLAXIS OF BENIGN PROSTATIC HYPERTROPHY

(57) Abstract

The present invention provides novel uses of compounds of general formula (I) wherein R¹, R⁴ and R⁵ are individually hydrogen, hydroxy, halogen, trifluoromethyl, C₁₋₆-alkyl, C₁₋₆-alkoxy or (tertiary amino)(C₁₋₆-alkoxy); and R² and R³ are individually hydrogen or C₁₋₆-alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of benign prostatic hypertrophy.



(I)

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | |
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Use of 3,4-diphenyl chromans for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of benign prostatic hypertrophy

FIELD OF THIS INVENTION

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The present invention relates to the use of compounds of the general formula I for the treatment of patients suffering from benign prostatic hypertrophy and prophylaxis hereof. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and
10 their pharmaceutical compositions.

BACKGROUND OF THIS INVENTION

Benign prostatic hypertrophy is an almost universal phenomenon in aging men. It
15 refers to a nodular enlargement of the gland due to hyperplasia of both glandular and stromal components. The incidence of this disease is only 8% during the fourth decade, but it reaches 50% in the fifth decade and 75% in the eighth decade. The disorder is not a major cause of death, but it is a leading cause of morbidity in elderly men. The pathogenesis is not well-understood, but dihydro-
20 testosterone together with increasing levels of estrogen which occur in men act synergistically to induce prostatic growth. The treatment is surgical, which, however, can only be offered to a small selected number of patients with this disease because the majority of men above age 60 have some degree of prostatic hyperplasia. No protecting factors other than castration have been identified
25 and no effective pharmacological treatment or prophylaxis exists.

Centchroman is a non-steroidal compound known to have antiestrogenic activity. It is in use in India as an oral contraceptive (see, for example, Salman et al., U.S. Patent Specification No. 4,447,622; Singh et al., Acta Endocrin (Copenh) 126
30 (1992), 444 - 450; Grubb, Curr Opin Obstet Gynecol 3 (1991), 491 - 495; San-
karan et al., Contraception 9 (1974), 279 - 289; Indian Patent Specification No.

129187). Centchroman has also been investigated as an anti-cancer agent for treatment of advanced breast cancer (Misra et al., Int J Cancer **43** (1989), 781 - 783. Recently, centchroman as a racemate has been found as a potent cholesterol lowering pharmaceutical expressed by a significant decrease of the serum concentrations (S.D. Bain et al., J Min Bon Res **9** (1994), S 394).

U.S. patent 5,453,442 describes methods of lowering serum cholesterol and inhibiting smoother muscle cell proliferation in humans and inhibiting uterine fibroid disease and endometriosis in women by administering compounds of formula I as shown therein. Furthermore, US patent 5,280,040 describes methods and pharmaceutical compositions for reducing bone loss using 3,4-diaryl chromans and their pharmaceutically acceptable salts. There is no disclosure in the patents of using the compounds to treat or prevent benign prostatic hypertrophy.

One object of the present invention is to provide compounds which can effectively be used in the treatment or prophylaxis of benign prostatic hypertrophy.

BRIEF DESCRIPTION OF THIS INVENTION

It has, surprisingly, been found that compounds of the general formula I as stated in claim 1 can be used in the treatment or prophylaxis of benign prostatic hypertrophy.

DETAILED DESCRIPTION OF THIS INVENTION

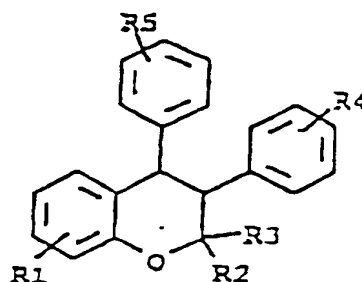
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The present invention is based in part on the discovery that a representative 3,4-diarylchroman, centchroman (3,4-trans-2,2-dimethyl-3-phenyl-4-[p-(beta--pyrrolidinoethoxy)phenyl]-7-methoxychroman) is effective against benign prostatic hypertrophy, inter alia in rats. An increased prostate weight is the cardinal observation seen in patients with prostatic hypertrophy, hence these data thus

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indicate that the 3,4-diarylchromans are useful as therapeutic agents against benign prostatic hypertrophy in mammals, including primates such as humans.

Within the present invention, compounds of formula I or their pharmaceutically acceptable salts

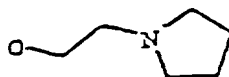


are used for the treatment or prophylaxis of benign prostatic hypertrophy in a patient.

Within formula I, R^1 , R^4 and R^5 are individually hydrogen, hydroxy, halogen, trifluoromethyl, C_{1-6} -alkyl, C_{1-6} -alkoxy or (tertiary amino)(C_{1-6} -alkoxy); and R^2 and R^3 are individually hydrogen or a C_{1-6} -alkyl. As used herein, the term " C_{1-6} -alkyl" includes straight and branched chain alkyl radicals containing from 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-amyl, sec-amyl, n-hexyl, 2-ethylbutyl, 2,3-dimethylbutyl and the like. The term " C_{1-6} -alkoxy" includes straight and branched chain alkoxy radicals containing from 1 to 6 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, n-amyloxy, sec-amyloxy, n-hexyloxy, 2-ethylbutoxy, 2,3-dimethylbutoxy and the like. "Halogen" includes chloro, fluoro, bromo and iodo. Herein, the term "(tertiary amino)(C_{1-6} -alkoxy)" is a C_{1-6} -alkoxy group which is substituted by a tertiary amino radical. The tertiary amino radical may be a N,N-dialkylamine such as a N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino

and N,N-dibutylamino or a polymethyleneimine, e.g., piperidine, pyrrolidine, N-methylpiperazine or morpholine. Preferred compounds include those in which R¹ is C₁₋₆-alkoxy; R² and R³ are C₁₋₆-alkyl, especially methyl; R⁴ is hydrogen; and R⁵ is (tertiary amino)(C₁₋₆-alkoxy) of the polymethyleneimine type. Within particularly preferred embodiments, R¹ is in the 7-position and is C₁₋₆-alkoxy, particularly methoxy; each of R² and R³ is methyl, R⁴ is hydrogen, and R⁵ is in the 4-position and is a (tertiary amino)(C₁₋₆-alkoxy) radical such as 2-(pyrrolidin-1-yl)ethoxy with formula II

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(II)

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To be included by this invention are all pharmaceutically acceptable salts of the mentioned compounds of formula I.

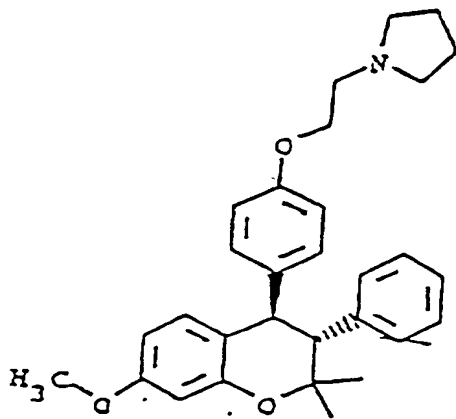
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It is preferred to use the compounds of formula I in the transconfiguration. These compounds may be used as racemic mixtures, or the isolated d- or l- enantiomers may be used. The trans-l-enantiomers are more preferred.

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A particularly preferred compound for use within the present invention is centchroman having the formula IV

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(IV)

Although only one enantiomer is shown, it will be understood that the formula IV is used herein to designate the transconfiguration of the 3- and 4-phenyl groups and that both the d- and l-enantiomers, as well as the racemic mixture, are included.

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3,4-diarylchromans are prepared according to known methods, such as those disclosed in U.S. Patent Specification No. 3,340,276 to Carney et al., U.S. Patent Specification No. 3,822,287 to Bolger, and Ray et al., J Med Chem **19** (1976), 276 - 279, the contents of which are incorporated herein by reference. Conversion of the cis isomer to the trans configuration by means of an organometallic base-catalyzed rearrangement is disclosed in U.S. Patent Specification No. 3,822,287. The optically active d- and l-enantiomers may be prepared as disclosed by Salman et al. in U.S. Patent Specification No. 4,447,622 (incorporated herein by reference) by forming an optically active acid salt which is subjected to alkaline hydrolysis to produce the desired enantiomer. If R₂ is different from R₃ and R₄ is different from R₅, the general formula I covers 8 optical isomers.

Within the present invention, 3,4-diarylchromans of formula I may be prepared in the form of pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

3,4-diarylchromans of formula I and their salts are useful within human and veterinary medicine, for example, in the treatment of patients suffering from benign

prostatic hypertrophy. For use within the present invention, 3,4-diarylchromans of formula I and their pharmaceutically acceptable salts are formulated with a pharmaceutically acceptable carrier to provide a medicament for parenteral, oral, nasal, rectal, subdermal or intradermal or transdermal administration according to conventional methods. Formulations may further include one or more diluents, fillers, emulsifiers, preservatives, buffers, excipients, etc. and may be provided in such forms as liquids, powders, emulsions, suppositories, liposomes, transdermal patches, controlled release, dermal implants, tablets, etc. One skilled in this art may formulate the compounds of formula I in an appropriate manner, and in accordance with accepted practices, such as those disclosed in Remington's Pharmaceutical Sciences, Gennaro, ed., Mack Publishing Co., Easton, PA, 1990.

Oral administration is preferred. Thus, the active compound of formula I is prepared in a form suitable for oral administration, such as a tablet or capsule. Typically, a pharmaceutically acceptable salt of the compound of formula I is combined with a carrier and moulded into a tablet. Suitable carriers in this regard include starch, sugars, dicalcium phosphate, calcium stearate, magnesium stearate and the like. Such compositions may further include one or more auxiliary substances, such as wetting agents, emulsifiers, preservatives, stabilizers, colouring additives, etc.

Pharmaceutical compositions containing a compound of formula I may be administered one or more times per day or week. An effective amount of such a pharmaceutical composition is the amount that provides a clinically significant effect against benign prostatic hypertrophy. Such amounts will depend, in part, on the particular condition to be treated, age, weight, and general health of the patient, and other factors evident to those skilled in the art. A typical daily dose will contain a nontoxic dosage range of from about 0.001 to about 75 mg/kg patient per day of a compound of the present invention.

The pharmaceutical compositions containing a compound of formula I may be administered in unit dosage form one or more times per day or week. In the alternative, they may be provided as controlled release formulations suitable for dermal implantation. Implants are formulated to provide release of active compound over the desired period of time, which can be up to several years. Controlled-release formulations are disclosed by, for example, Sanders et al., J Pharm Sci 73 (1964), 1294 - 1297, 1984; U.S. Patent Specification No. 4,489,056; and U.S. Patent Specification No. 4,210,644, which are incorporated herein by reference.

The following examples are offered by way of illustration, not limitation.

Examples of preferred compounds of formula I are centchroman as a racemic mixture and as isolated l-centchroman and d-centchroman enantiomers. Furthermore, 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman is a preferred compound. The more preferred compound is isolated l-centchroman (l-3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman).

Examples of pharmaceutically acceptable acid addition salts are salts with non-toxic acids, either inorganic acids such as hydrochloric acid, sulphuric acid and phosphoric acid, or organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, succinic acid, gluconic acid, lactic acid, citric acid, ascorbic acid, benzoic acid, embonic acid, methanesulphonic acid and malonic acid.

The present invention is further illustrated by the following examples which, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

Example 1

Sixty sexually mature male Sprague-Dawley rats were assigned to one of the following five treatment groups (12 rats per group): 1) saline, 2) l-centchroman 0.025 mg/kg/day, 3) l-centchroman 0.125 mg/kg/day, 4) l-centchroman 0.625 mg/kg/day and 5) l-centchroman 3.125 mg/kg/day. The doses were administered three times per week for 13 weeks by oral gavage. At the conclusion of the experiment and autopsy was performed, the prostate gland and testes were isolated and weighed.

10 L-centchroman had no effect on the average testis weight between the groups. However, a marked and dose-dependent effect on the prostate gland was observed as illustrated in Table 1.

15 Table 1. Effect of l-centchroman on prostate gland weight in Sprague-Dawley rats

| Treatment | Prostate gland (g) |
|-------------------------------|--------------------|
| Saline | 0.639 \pm 0.239 |
| l-centchroman 0.025 mg/kg/day | 0.669 \pm 0.149 |
| l-centchroman 0.125 mg/kg/day | 0.472 \pm 0.126* |
| l-centchroman 0.625 mg/kg/day | 0.430 \pm 0.122* |
| l-centchroman 3.125 mg/kg/day | 0.368 \pm 0.124* |

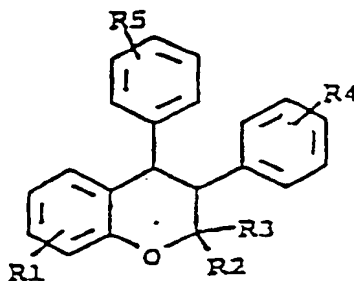
Values are mean \pm SD. * indicate significant reduction of prostate gland weight compared to saline treated rats.

CLAIMS

1. The use of compounds of the general formula I

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(I)

- 15 wherein R1, R4 and R5 are individually hydrogen, hydroxy, halogen, trifluoro-methyl, C₁₋₆-alkyl, C₁₋₆-alkoxy or (tertiary amino)(C₁₋₆-alkoxy); and R2 and R3 are individually hydrogen or C₁₋₆-alkyl, or as a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier for the manufacture of a pharmaceutical composition for the treatment or prophylaxis of benign pro-
- 20 static hypertrophy.

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2. The use, according to claim 1, wherein R1 in the compound used is C₁₋₆-alkoxy, R2 and R3 are C₁₋₆-alkyl, R4 is hydrogen and R5 is (tertiary amino) C₁₋₆-alkoxy.
3. The use according to any one of claims 1 or 2 wherein R1 is methoxy.
4. The use according to any one of claims 1-3 wherein R2 is methyl.
- 30 5. The use according to any one of claims 1-4 wherein R3 is methyl.

6. The use according to any one of claims 1-5 wherein R₄ is hydrogen.

7. The use according to any one of claims 1-6 wherein R₅ is a group as stated in formula II below:

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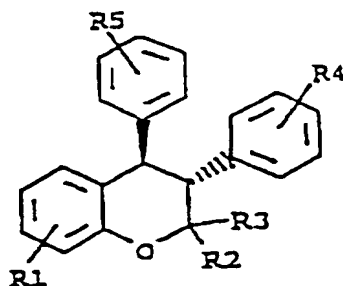


(II)

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8. The use according to any one of claims 1-7 wherein said compound is an isolated d- or l-enantiomer.

15 9. The use according to any one of claims 1-8 wherein said compound has the general formula III as stated below:



(III)

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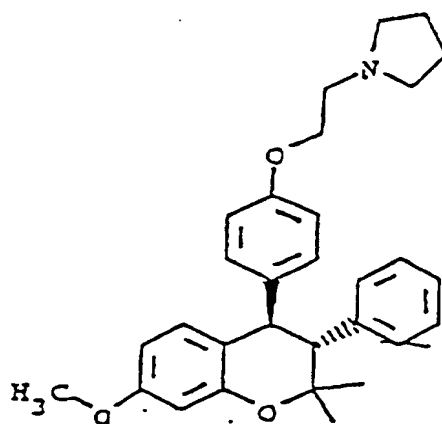
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wherein R₁, R₂, R₃, R₄ and R₅ each are as defined in above claim 1.

10. The use according to anyone of the preceding claims wherein said compound is 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-hydroxychroman.

5 11. The use according to anyone of the preceding claims wherein said compound is an isolated l-enantiomer.

12. The use according to claim 1 wherein said compound is centchroman
3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-
10 methoxychroman having the formula IV as stated below:



(IV)

13. The use according to claim 12 wherein said compound is an isolated l-enantiomer of 3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(pyrrolidin-1-yl)ethoxy)phenyl]-7-methoxychroman.

14. The use according to any one of the preceding claims wherein said composition is in a form suitable for oral administration.

15. The use according to any one of the preceding claims wherein said compound is administered as a dose in a range from about 0.001 to 75 mg/kg patient per day.

16. The use according to any one of the preceding claims wherein said composition is administered one or more times per day or week.

5 17. The use according to any one of the preceding claims wherein said composition is in the form of a dermal implant.

18. Method for treatment and prophylaxis of benign prostatic hypertrophy comprising administering to a patient a clinically effective amount of a compound
10 of above formula I stated to be used in any of the preceding use claims, or a pharmaceutically acceptable salt thereof in an amount sufficient to treat or prevent benign prostatic hypertrophy.

19. A method of treating or preventing benign prostatic hypertrophy which
15 method comprises administering a clinically effective amount of compounds and pharmaceutically acceptable compositions, according to previous claims to a patient in need of such a treatment.

20. Any novel feature or combination of features described herein.
20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00011

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/40, A61K 31/35
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | US 4310523 A (FRIEDMUND NEUMANN), 12 January 1982 (12.01.82) ----- | 1-17 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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& document member of the same patent family

Date of the actual completion of the international search

12 March 1997

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK97/00011

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18-19
because they relate to subject matter not required to be searched by this Authority, namely:
A method for treatment of the human or animal body by therapy,
see rule 39.1.
2. ☒ Claims Nos.: 20
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 20 is obscure and does not clearly define the matter for which protection is sought, see Article 6.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

03/02/97

International application No.
PCT/DK 97/00011

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| US-A- 4310523 | 12/01/82 | AU-B- 528179 | 21/04/83 |
| | | AU-A- 4560479 | 25/10/79 |
| | | BE-A- 875634 | 17/10/79 |
| | | CA-A- 1134271 | 26/10/82 |
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| | | JP-B- 1005007 | 27/01/89 |
| | | JP-C- 1520155 | 29/09/89 |
| | | JP-A- 55013261 | 30/01/80 |
| | | LU-A- 81153 | 19/06/79 |
| | | NL-A- 7901961 | 19/10/79 |
| | | SE-B,C- 441977 | 25/11/85 |
| | | SE-A- 7903240 | 18/10/79 |
